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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/816,688	03/22/2001	Katherine A. High	CHOP-0026	5212

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WOODCOCK WASHBURN LLP
CIRA CENTRE, 12TH FLOOR
2929 ARCH STREET
PHILADELPHIA, PA 19104-2891

EXAMINER	
WHITEMAN, BRIAN A	

ART UNIT	PAPER NUMBER
1635	

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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	09/816,688	HIGH ET AL.	
	Examiner	Art Unit	
	Brian Whiteman	1635	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *18 August 2008*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1,2,13-37,41-49 and 56-84* is/are pending in the application.

4a) Of the above claim(s) *33,36,37,42-49,56-63 and 81* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1,2,13-32,34,35,41,64-80, 82-84* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Election/Restrictions

Claims 33, 36, 42-49, 56-63, and 81 are withdrawn from further consideration pursuant to 37 CFR 1.142(b) as being drawn to a non-elected invention and adenovirus, parvovirus, papilloma virus, reovirus, rotavirus, and herpes virus in claim 31 are withdrawn from further consideration pursuant to 37 CFR 1.142(b) as being drawn to a nonelected species, there being no allowable generic or linking claim. Election was made **without** traverse in the reply filed on 4/7/06.

Upon further consideration, claims 64-80 and 82-84 are rejoined the elected species and examined.

Priority

Applicant's claim for the benefit of a prior-filed application under 35 U.S.C. 119(e) or under 35 U.S.C. 120, 121, or 365(c) is acknowledged. Applicant has not complied with one or more conditions for receiving the benefit of an earlier filing date under 35 U.S.C. 119(e) as follows:

The later-filed application must be an application for a patent for an invention which is also disclosed in the prior application (the parent or original nonprovisional application or provisional application). The disclosure of the invention in the parent application and in the later-filed application must be sufficient to comply with the requirements of the first paragraph of 35 U.S.C. 112. See *Transco Products, Inc. v. Performance Contracting, Inc.*, 38 F.3d 551, 32 USPQ2d 1077 (Fed. Cir. 1994).

The disclosure of the prior-filed application, Application No. 60/191,331, fails to provide adequate support or enablement in the manner provided by the first paragraph of 35 U.S.C. 112 for one or more claims of this application. Instant claims 1, 2, 13-32, 34, 35, 41, 64-80, and 82-84: There is no written support for SEQ ID NO: 1 in '331. Thus, SEQ ID NO: 1 only enjoys priority to instant application filed on 3/22/01.

Claim Objections

Claims 81 and 82 are objected to because of the following informalities: the claims embrace a non-elected invention. Appropriate correction is required.

Claim 64 is objected to because of the following informalities: it is not apparent if SEQ ID NO: 1 is the sequence for RLRRLR or is an example of a sequence containing RLRRLR. Appropriate correction is required.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

The factual inquiries set forth in *Graham* **v.** *John Deere Co.*, 383 U.S. 1, 148 USPQ 459 (1966), that are applied for establishing a background for determining obviousness under 35 U.S.C. 103(a) are summarized as follows:

1. Determining the scope and contents of the prior art.

2. Ascertaining the differences between the prior art and the claims at issue.
3. Resolving the level of ordinary skill in the pertinent art.
4. Considering objective evidence present in the application indicating obviousness or nonobviousness.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

The functional limitation in claims 1, 16-18, and 64 (when expressed in an animal cell and secreted in active form) does not have patentable under a prior art rejection teaching a product with the same structure. See MPEP 2112.01 and 2122.

The functional limitations "wherein the animal cell is mammalian" in claims 15 and 66 and "wherein the mammalian cell is human" in claims 16 and 67 do not have patentable under a prior art rejection. See MPEP 2112.01 and 2122.

The limitation "instructions for expressing the modified blood clotting factor in vitro, ex vivo, or in vivo" in claims 35 and 83 does not have patentable under a prior art rejection. See MPEP 2112.01 (III) and 2122.

Where, as here, the claimed and prior art products are identical or substantially identical, or are produced by identical or substantially identical processes, the PTO can require an applicant to prove that the prior art products do not necessarily or inherently possess the characteristics of his claimed product. See In re Ludtke 441 F.2d 660, 169 USPQ 563 (CCPA 1971). Whether the rejection is based on "inherency" under 35 USC 102, or "prima facie obviousness" under 35 USC 103, jointly or alternatively, the burden

of proof is the same, and its fairness is evidenced by the PTO's inability to manufacture products or to obtain and compare prior art products. In re Best, Bolton, and Shaw, 195 USPQ 430, 433 (CCPA 1977) citing In re Brown, 59 CCPA 1036, 459 F.2d 531, 173 USPQ 685 (1972).

Claims 1, 2, 13-25, 29-32, 34, 35, 41, 64-73, 77-80, and 82-84 are rejected under 35 U.S.C. 103(a) as being unpatentable over Scaria et al. (US 20030229036) taken with Wolf (US 5,795,863) in further view of Miller et al (US 6,924,365).

Scaria teaches viral vectors (e.g., AAV) comprising a promoter operably linked to a nucleic acid encoding a modified Factor VII comprising a PACE/furin cleavage site replacing the activation cleavage site of Factor VII and a pharmaceutical acceptable carrier (pages 1-11). Scaria further teaches Factor IX (pages 3 and 4). The vector encodes a modified version of Factor VII such that it leads to generation of (or can be converted to) activated Factor VII in vivo (page 3). Scaria teaches that activation of Factor VII to Factor VIIa involves proteolytic cleavage at a single bond between arginine 152 and isoleucine 153 (page 2) resulting in a heavy and light chain. Factor VII can be from any mammalian source, including human (page 4). The Factor VII can have one or more conservative amino acids (page 4). However, Scaria does not specifically teach the PACE cleavage site comprises SEQ ID NO: 1.

However, at the time the invention was made, Wolf teaches making a coagulation factor comprising a PACE cleavage site comprising SEQ ID NO: 1 (columns 31-32).

In addition, at the time the invention was made, Miller teaches a nucleic acid sequence that directs synthesize of an optimized message which encodes a coagulation factor protein having a recognition site for an intracellular protease of the PACE/furin class, e.g., X-Arg-X-X-Arg (columns 5-6 and 20). Miller teaches that viral vectors (e.g., AAV) were well known to one of ordinary skill in the art for delivering a nucleic acid to a cell (column 22).

It would have been *prima facie* obvious to a person of ordinary skill in the art at the time the invention was made to combine the teaching of Scaria taken with Wolf in further view of Miller, namely to produce a vector encoding a Factor VII or Factor IX polypeptide having a proteolytic cleavage site comprising SEQ ID NO: 1. One of ordinary skill in the art would have been motivated to combine the teaching to provide an active amount of Factor VII or Factor IX and for directing synthesis of an optimized message which encodes a coagulation protein factor. "The combination of familiar elements according to known methods is likely to be obvious when it does no more than yield predictable results." See ***KSR v. Teleflex***, 550 U.S. ___, 127 S. Ct. 1727 (2007).

It would have been *prima facie* obvious to a person of ordinary skill in the art at the time the invention was made to combine the teaching of Scaria taken with Wolf in further view of Miller, namely to insert the proteolytic cleavage site is introduced between 152 and 153 of Factor VII. One of ordinary skill in the art would have been motivated to combine the teaching to substitute the native cleavage site with the PACE cleavage site provide an active amount of Factor VII. See ***KSR v. Teleflex***.

It would have been *prima facie* obvious to a person of ordinary skill in the art at the time the invention was made to combine the teaching of Scaria taken with Wolf in further view of Miller, namely to produce the composition comprising a viral vector selected from an adeno associated adenovirus (AAV). One of ordinary skill in the art would have been motivated to combine the teaching to sufficiently express Factor VII or Factor IX in a liver cell. See ***KSR v. Teleflex***.

Therefore the invention as a whole would have been *prima facie* obvious to one ordinary skill in the art at the time the invention was made.

Applicant's arguments filed 8/18/08 have been fully considered but they are not persuasive.

In response to applicant' s argument that the examiner has failed to teach the teaching of the prior art as a whole, the argument is not found persuasive because the only teaching of Wolf required for the 103(a) rejection is that a proteolytic cleavage site comprising SEQ ID NO: 1 can be successfully used to make a coagulation protein factor. Wolf is not teaching that by using a proteolytic cleavage site comprising SEQ ID NO: 1 results in an inactive Factor X. If this was the case, then applicant would be arguing that there claimed invention is not enabled in view of the teaching of Wolf. Instead Wolf is teaching modifying the amino acid sequence of Factor X and using a proteolytic cleavage site comprising SEQ ID NO: 1 to cleave the modified Factor X. Furthermore, Scaria teaches the claimed product, except for SEQ ID NO: 1. One of ordinary skill in the art would use the proteolytic cleavage comprising SEQ ID NO: 1 to produced the claimed composition to express Factor VII in a liver cell. This is based on

a simple substitution of one known element for another to obtain a predictable result. See MPEP 2143 and also see In re O 'Farrell, 853 F.2d 894, 7 USPQ2d 1673 (Fed. Cir. 1988).

In response to applicant's arguments against the references individually, one cannot show nonobviousness by attacking references individually where the rejections are based on combinations of references. See *In re Keller*, 642 F.2d 413, 208 USPQ 871 (CCPA 1981); *In re Merck & Co.,* 800 F.2d 1091, 231 USPQ 375 (Fed. Cir. 1986). This is the case here. The combination of Scaria, Miller, and Wolf teach the claimed invention, not just Wolf. The only element missing from Scaria is a proteolytic cleavage site comprising SEQ ID NO: 1 which is taught by Wolf and Miller.

Claims 1, 24, 28, 64, 72, 73, and 76 are rejected under 35 U.S.C. 103(a) as being unpatentable over Scaria et al. taken with Wolf in further view of Miller as applied to claims 1, 2, 13-25, 29-32, 34, 35, 41, 64-71, 77-80, and 82-84 above, and further in view of Amalfitano et al. (US 6,328,958).

Scaria taken with Wolf in further view of Miller do not specifically teach using an EF-1-alpha promoter in the composition.

However, at the time the invention was made, Amalfitano teaches a heterologous nucleotide sequence (e.g., clotting factor) operatively associated with a cytomegalovirus (CMV) major immediate-early promoter, an albumin promoter, an Elongation Factor 1-.alpha. (EF1-.alpha.) promoter, a P.gamma.K promoter, a MFG promoter, or a Rous sarcoma virus promoter. See columns 19-20.

It would have been *prima facie* obvious to a person of ordinary skill in the art at the time the invention was made to combine the teaching of Scaria taken with Wolf and Miller in further view of Amalfitano, namely to produce the composition comprising an EF1-alpha promoter. One of ordinary skill in the art would have been motivated to combine the teaching to sufficiently express Factor VII or Factor IX in a cell. See ***KSR v. Teleflex***.

Therefore the invention as a whole would have been *prima facie* obvious to one ordinary skill in the art at the time the invention was made.

Applicant's arguments filed 8/18/08 have been fully considered but they are not persuasive for the reasons set forth in the previous response to applicant's argument against the 103(a) rejection based on Scaria taken with Wolf and Miller.

Claims 1, 24, 26, 27, 64, 72, 74, and 75 are rejected under 35 U.S.C. 103(a) as being unpatentable over Scaria et al. taken with Wolf in further view of Miller as applied to claims 1, 2, 13-25, 29-32, 34, 35, 41, 64-71, 77-80, and 82-84 above, and further in view of Kochanek (US 5,981,225).

Scaria taken with Wolf and Miller do not specifically teach using a skeletal muscle actin or muscle creatine kinase (MCK) promoter in the composition.

However, at the time the invention was made, the use of the MCK promoter will lead to tissue specific expression of a foreign gene (column 13).

It would have been *prima facie* obvious to a person of ordinary skill in the art at the time the invention was made to combine the teaching of Scaria taken with Wolf and

Miller in further view of Kochanek, namely to produce the composition comprising a skeletal muscle actin or muscle creatine kinase promoter. One of ordinary skill in the art would have been motivated to combine the teaching to selectively express Factor VII or Factor IX in a desired cell. See ***KSR v. Teleflex***.

Therefore the invention as a whole would have been *prima facie* obvious to one ordinary skill in the art at the time the invention was made.

Applicant's arguments filed 8/18/08 have been fully considered but they are not persuasive for the reasons set forth in the previous response to applicant's argument against the 103(a) rejection based on Scaria taken with Wolf and Miller.

Double Patenting

The nonstatutory double patenting rejection is based on a judicially created doctrine grounded in public policy (a policy reflected in the statute) so as to prevent the unjustified or improper timewise extension of the "right to exclude" granted by a patent and to prevent possible harassment by multiple assignees. A nonstatutory obviousness-type double patenting rejection is appropriate where the conflicting claims are not identical, but at least one examined application claim is not patentably distinct from the reference claim(s) because the examined application claim is either anticipated by, or would have been obvious over, the reference claim(s). See, e.g., *In re Berg*, 140 F.3d 1428, 46 USPQ2d 1226 (Fed. Cir. 1998); *In re Goodman*, 11 F.3d 1046, 29 USPQ2d 2010 (Fed. Cir. 1993); *In re Longi*, 759 F.2d 887, 225 USPQ 645 (Fed. Cir. 1985); *In re Van Ornum*, 686 F.2d 937, 214 USPQ 761 (CCPA 1982); *In re Vogel*, 422 F.2d 438, 164 USPQ 619 (CCPA 1970); and *In re Thorington*, 418 F.2d 528, 163 USPQ 644 (CCPA 1969).

A timely filed terminal disclaimer in compliance with 37 CFR 1.321(c) or 1.321(d) may be used to overcome an actual or provisional rejection based on a nonstatutory double patenting ground provided the conflicting application or patent either is shown to be commonly owned with this application, or claims an invention made as a result of activities undertaken within the scope of a joint research agreement.

Effective January 1, 1994, a registered attorney or agent of record may sign a terminal disclaimer. A terminal disclaimer signed by the assignee must fully comply with 37 CFR 3.73(b).

Claims 1, 2, 13-23, 29-32, 34, 35, 41, 64-73, 78-80, and 82-84are rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claims 1-7 of U.S. Patent No. 7,211,558 in view of Scaria et al. (US 2003/0229036). The claims of '558 teach a nucleic acid encoding a modified coagulation factor (Factor VIII) comprising a proteolytic cleavage site comprising RKRRKR. However, the claims from '558 do not specifically teach a Factor VII or Factor IX comprises the proteolytic cleavage site.

However, at the time the invention was made, Scaria teaches vector (AAV, retroviral, plasmid, and lentiviral) comprising a promoter operably linked to a nucleic acid encoding a modified Factor VII comprising a PACE/furin cleavage site replacing the activation cleavage site of Factor VII and a pharmaceutical acceptable carrier (pages 1-11). Scaria teaches Factor IX (pages 3 and 4). The vector encodes a modified version of Factor VII such that it leads to generation of (or can be converted to) activated Factor VII in vivo (page 3). Scaria teaches that activation of Factor VII to Factor VIIa involves proteolytic cleavage at a single bond between arginine 152 and isoleucine 153 (page 2) resulting in a heavy and light chain. Factor VII can be from any mammalian source, including human (page 4). The Factor VII can have one or more conservative amino acids (page 4).

It would have been *prima facie* obvious to a person of ordinary skill in the art at the time the invention was made to combine the claims of '558 and Scaria, namely to produce a nucleic acid encoding a modified Factor VII or Factor IX comprising a

proteolytic cleavage site comprising RKRRKR. One of ordinary skill in the art would have been motivated to combine to produce an active form of Factor VII.

Therefore the invention as a whole would have been *prima facie* obvious to one ordinary skill in the art at the time the invention was made.

Applicant's arguments filed 8/18/08 have been fully considered but they are not persuasive because the non-elected species has been rejoined with the elected species.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Brian Whiteman whose telephone number 571-272-0764. The examiner can normally be reached on from 6:30 to 4:00 (Eastern Standard Time). The examiner can also be reached on alternate Fridays.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor James Douglas Schultz can be reached on 571-272-0763. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should

you have questions on access to the Private PAIR system, contact the Electronic

Business Center (EBC) at 866-217-9197 (toll-free).

/Brian Whiteman/
Primary Examiner, Art Unit 1635